REMARKS

Claims 49-54, 56-62 and 64-65 are presently pending and under examination. Claims 49, 53, 54, 57 and 65 have been amended. New claims 66 and 67 have been added. Support for the amendments and new claims can be found throughout the application as filed. Support for the amendment to claims 1 and 57 can be found at, for example, page 6, first through fourth paragraphs. Support for the amendment to claims 54 and 65 and for new claims 66 and 67 can be found at, for example, page 11, lines 1-7; page 12, lines 27-29; page 13, lines 1-4 and in Figure 2. Claims 53 and 54 also have been amended to correct an obvious typographical error. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicants have reviewed the Office Action issued December 22, 2006, and respectfully traverse all grounds of rejection for the reasons that follow.

Rejections Under 35 U.S.C. § 101

Claims 49-54, 56-62 and 64-65 stand rejected under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. The Office alleges that the claimed invention lacks either a physical transformation or fails to produce a useful, concrete and tangible result. With respect to the latter assertion, the Office alleges that the claimed method fails to require the result to be output, saved or displayed in a tangible form.

Applicants respectfully disagree. The claims are directed to methods of producing a genome specific stoichiometric matrix from substrates, products and stoichiometry. While not conceding that the claims are directed to non-statutory patentable subject matter, Applicants have amended the claims to recite providing an output of the claimed genome specific stoichiometric matrix to a user. Therefore, the claims clearly recite both a physical transformation and a useful, concrete and tangible result since an output is provided to a user and since the provided genome specific stoichiometric matrix can be analyzed, for example, for gene functions and microbe growth. In light of this amendment, this ground of rejection is moot and Applicants respectfully request its withdrawal.

Rejections Under 35 U.S.C. § 112

Claims 49-54, 56-62 and 64-65 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. Applicant addresses each rejection in turn below.

With respect to claims 49 and 57, the Examiner alleges that the disclosure of "most" or "nearly" the entire genome fails to convey the concept of inclusion a number of sequences sufficient to produce an *in silico* representation.

The test for written description is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed. *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) (*citing Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Sufficiency is found where the specification adequately describes the claimed invention so that one skilled in the art can recognize what is claimed. *Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316, 1328 (Fed. Cir. 2002).

Applicant respectfully disagrees with this ground of rejection. Nevertheless, submitted herewith is a declaration by Dr. Jeremy S. Edwards attesting that the description in the application adequately conveys to one skilled in the art that only a sufficient number of genes which is sufficient to produce the claimed representation needs to be included in the representation (Exhibit A). In light of this declaration, Applicant maintains that the specification satisfies the written description requirements of the first paragraph of § 112 and respectfully requests withdrawal of this ground of rejection.

Claim 53 is alleged not to require formulating a general linear programming problem representing the *in silico* strain and, therefore, in comparison to Figure 2, allegedly fails to be supported by the application. In support, the Examiner alleges that the concept of step 64 in Figure 2 is not synonymous with combining the metabolic demands and uptake rates with the stoichiometric matrix.

Applicant respectfully points out that "[t]o comply with written description, it is not necessary that the application describe the claimed invention in *ipsis verbis*." *Application of Edwards*, 568 F.2d 1349, 1351-52 (C.C.P.A. 1978); *see also Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376, (Fed.Cir. 2002) ("the disclosure as originally filed does not

have to provide *in haec verba* support for the claimed subject matter at issue"); *New Railhead Mfg. L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1296 (Fed. Cir. 2002) ("[i]dentity of description is not necessary").

Applicant has never asserted the concept alleged by the Examiner nor does the application synonymize combining metabolic demands, uptake rates and a stoichiometric matrix with the additional step of formulating a general linear programming problem to produce an *in silico* strain. Rather, the application teaches six exemplary steps to arrive at an *in silico* strain. Teaching all six steps is sufficient description to show Applicant was in possession of each and every step, either individually or in combination, and in possession of the representations resulting from each step, either individually or in combination. Before moving to a subsequent step, it necessarily follows that the preceding step produces a representation from which the following step can be added to. It is not necessary for Applicant to have identity of description expressly stating that a representation results from each step, especially when, as here, a new representation necessarily results from each of the described steps.

The application expressly describes each step exemplified in Figure 2 (see, for example, page 8, para. 2 through page 11, line 5). From these descriptions it is clear that a representation results from each step in the process that can be added to, or further processed, in a subsequent step.

For example, the application teaches "[a]fter the genome specific stoichiometric matrix is defined at state 58, the metabolic demands placed on the organism are calculated." (*Id.*, page 9, para. 2; emphasis added). It inherently follows that if an action is described to occur after a previous step, then the representation of the previous step has been sufficiently completed.

Similarly, the application teaches that "[t]he process 50 then moves to state 62 to perform several experiments that determine the uptake rates and maintenance requirements for the organism." (*Id.*, page 9, para. 3; emphasis added).

Likewise, the application teaches "[n]ext, the process 50 moves to a state 64 wherein information regarding the metabolic demands and uptake rates obtained at state 62 are combined

with the genome specific stoichiometric matrix of step 8 [*sic*] together fully define the metabolic system using flux balance analysis (FBA)." (*Id.*, page 10, para. 1; emphasis added).

Where a process performs a step on an *in silico* representation "after" some act is completed or "then moves to" or "next moves to" a further step, the process describes an intermediate representation resulting from the prior step or steps. By express description of each and every step in the process exemplified in Figure 2, Applicant has provided sufficient written description for the claimed process that either starts or stops at any step in the process. Therefore, Applicant is entitled to claim, and has adequate written description, for the representations produced from some or all of the six exemplary steps along the process for producing an *in silico* strain. Claim 53 is directed to the first five of the six exemplified steps. Accordingly, withdrawal of this ground of rejection is respectfully requested.

With respect to claims 54 and 65, directed to a method of simulating a metabolic capability of an *in silico* representation of microbe, the Examiner alleges that the cited support discloses metabolic capabilities and simulations which require manipulations of constraints or genes and that such manipulations are absent from the claims. The Examiner also alleges that claim 54 lacks the step of solving a linear programming problem and points out that claim 65 does not recite the additional step of performing flux balance, although it appears to parallel claim 54.

Claim 54 is directed to a method of simulating a metabolic capability of an *in silico* strain by performing flux balance analysis. Performing flux balance analysis constitutes solving a linear programming problem. Therefore, the assertion that this step lacks written description because it fails to recite solving a linear programming problem is unsupported. Although adequately supported as written, Applicant has amended claims 54 and 65 to explicitly recite incorporating a general linear programming problem. The step of performing flux balance analysis also has been included in claim 65. These amendments differentiate the method of producing an *in silico* strain as recited in new claims 66 and 67 from the method of simulating a metabolic capability of such an *in silico* strain.

Applicant respectfully disagrees with the Examiner's assertion that determination of a metabolic capability requires manipulations of constraints or genes. The application discloses

that the metabolic capabilities are complete and can be determined once, for example, the general linear programming problem has been incorporated. In comparison, the application further discloses that evaluating the metabolic capabilities under given sets of conditions defines the metabolic phenotype under those particular conditions. Exemplary sets of conditions include genetic deletions and/or resources present in the strain's *in vivo* environment. In particular, the application discloses:

> The solutions to Equation 1 lie in a restricted region. This subspace defines the capabilities of the *metabolic genotype* of a given organism, since the allowable solutions that satisfy Equation 1 and any constraints placed on the fluxes of the system define all the metabolic flux distributions that can be achieved with a particular set of metabolic genes.

Id., page 11, lines 1-5 (emphasis added; italics original).

Therefore, the application teaches that the metabolic capabilities of a metabolic genotype having, for example, a particular set of genes is defined by a subspace corresponding to the allowable solutions to a general linear programming problem and any constraints placed on the system's fluxes. This description lacks any requirement for manipulating constraints. Rather, as described further below, changing the gene set or constraints will change the capabilities because the metabolic phenotype has changed.

In comparison, the passage cited at page 13 appears to be interpreted out of context because this description discloses exemplary applications of the claimed *in silico* strains "to determine the affects of the removal or addition of particular genes and their associated reactions to the composition of the metabolic genotype on the range of possible metabolic phenotypes" (page 13, lines 8-10; emphasis added). For example, the sentences immediately preceding the cited passage state:

> The *in silico* strain can then be used to study theoretical metabolic capabilities by simulating any number of conditions . . . The process 50 of formulating the *in silico* strain and simulating its behavior using linear programming techniques terminates at an end state 66.

Id., page 13, lines 1-4 (emphasis added).

This passage clearly describes that an *in silico* strain is complete and can be used for simulating behavior once steps of the claimed process are performed because it can then be used to study other capabilities or simulate other behavior. Further, the application explicitly teaches that utilization of a particular metabolic genotype under a given set of conditions, such as those cited at page 13, corresponds to a metabolic phenotype and that objectives can be chosen to explore the best use of the metabolic network within a given metabolic genotype, when the application discloses:

> The particular utilization of the metabolic genotype can be defined as the *metabolic phenotype* that is expressed under those particular conditions. Objectives for metabolic function can be chosen to explore the 'best' use of the metabolic network within a given metabolic genotype.

Id., page 11, lines 6-9 (emphasis added; italics original).

The above exemplary descriptions disclose that once a metabolic genotype is constructed a particular *in silico* strain can be generated by following the claimed method. Changing a gene within the metabolic genotype results in a new metabolic genotype that generates a new strain. Therefore, once an *in silico* strain has been constructed for a particular metabolic genotype, it can be used to simulate the capabilities of the initially constructed strain or interrogated by further simulation of genetic deletions to analyze and interpret genotype-phenotype relationships. As described in the passage cited at page 13, these additional manipulations are for further analysis. Accordingly, such interrogations are not required to simulate the capabilities of the initially constructed strain. Rather, they are used to explore the range of phenotypes by making a change and simulating the capabilities of the new strain. Therefore, the application provides sufficient written description for the invention as claimed and withdrawal of this ground of rejection is respectfully requested.

Further with respect to claim 65, the Examiner alleges that it appears to repeat the steps of the method of claim 61, but that the application appears to lack a basis for this repetition.

Applicant respectfully refers the Examiner to the arguments above where it is noted that claim 65 parallels claim 54 and is directed to a method of simulating a metabolic capability of an *in silico* strain of a microbe. The step of performing flux balance analysis on the *in silico* strain

for simulating the capabilities has been added. In light of this amendment, this ground of rejection is moot and its withdrawal is respectfully requested.

Claims 49-54, 56-62, 64 and 65 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. The Examiner alleges the specification fails to provide guidance as to what number of genes is sufficient to produce an *in silico* representation or fails to disclose objective criteria for evaluating gene number sufficiency.

Applicant respectfully disagrees. Nevertheless, submitted herewith is a declaration by Dr. Jeremy S. Edwards attesting that the application provides sufficient teachings and guidance for one skilled in the art to select a number of genes sufficient to produce an *in silico* representation (Exhibit B). In light of this declaration, Applicant maintains that the specification satisfies the enablement requirement of the first paragraph of § 112 and respectfully request withdrawal of this ground of rejection.

Rejections Under 35 U.S.C. § 102

Claims 49-51, 53-54, 56-59, and 61-65 stand rejected under 35 U.S.C. § 102(b) as anticipated by Schilling et al. allegedly because the cited reference describes all elements of the claimed.

Applicant respectfully maintains that the claims as filed in the continuation application are adequately supported as of the priority date. Applicant refers the Examiner to the arguments above and previously of record directed to adequate written description. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 52 and 60 stand rejected under 35 U.S.C. § 103(a) as obvious over Schilling et al. as applied to claims 49-51, 53-59 and 61-65 above and further because the use of BLAST would have been obvious to those skilled in the art allegedly because it is a well known search tool.

While not conceding that Schilling et al. teach or suggest the claimed invention, Applicant has set forth previously that the claims as filed in the continuation application are

adequately supported as of the priority date. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

Claims 49-54, 56-62 and 64-65 remain rejected under 35 U.S.C. § 103(a) as being obvious over Blattner et al., Pennisi, Edwards et al. (1997) and Pramanik et al. The Examiner alleges that it would have been obvious to produce a stoichiometric matrix and an *in silico* model of *E. coli* and *H. influenzae* according to Pramanik et al. using the descriptions in Blattner et al. and Pennisi et al. allegedly because such models would have been of interest and within the skill of the art to produce as described by Edwards et al. The Examiner appears to summarily reject Applicant's argument that Pramanik et al. teach away from using models that are not produced from biochemical information by merely concluding that biochemical information was available.

Applicant respectfully requests the Examiner to provide reasons why Pramanik et al. does not teach away from the claimed invention. The Examiner continues to cite Pramanik et al. allegedly for describing *E. coli* and *H. influenzae in silico* models (see, for example, Office Action, page 7, para. 5 ("it would have been obvious to produce a stoichiometric matrix and *in silico* model of the microbes *E. coli* and *H. influenzae* according to Pramanik et al."). However, the Examiner fails to address Applicant's showing that Pramanik et al. teach away from the claimed invention. The only response to Applicant's showing on record is, for example:

> [T]hese concerns are not applicable with respect to the art applied as biochemical information was known at the time of the invention for the organisms suggested.

Office Action mailed December 22, 2006, page 7, para. 2.

This response contradicts the reasons why Pramanik et al. is cited (see above). Further, Applicant respectfully points out to the Examiner that <u>any</u> reference teaching away from the claimed invention can be used to rebut a rejection based on obviousness. *In re Kahn*, Case No. 04-1616, slip op. at 19-20 (Fed. Cir. March 22, 2006) (*quoting In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (reference teaches away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."). The Examiner is not at liberty to rely on one portion of a reference in support of one proposition and ignore other

teachings in the reference which go against the rejection as is implied by the above rationale. Therefore, the teaching away Applicant has pointed out must be considered.

In light of the teaching away in Pramanik et al., Applicant maintains that the invention as claimed is unobvious over the cited art. Therefore, withdrawal of this ground of rejection is respectfully requested.

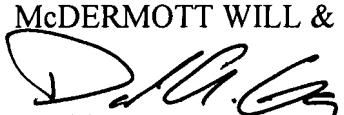
CONCLUSION

In light of the Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP



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